REMARKS

Claims 1-21 are pending in the present Application. Claims 10-21 have been withdrawn from consideration; Claim 2 has been cancelled, Claims 1, 3 and 4 have been amended, leaving Claims 1 and 3-9 for consideration upon entry of the present Amendment.

Support for the amendment to claim 1 can be found in claim 2 as originally filed.

Claim 3 has been amended merely to change its dependency.

Claim 4 has been amended to correct a typographical error.

Reconsideration and allowance of the claims are respectfully requested in view of the above amendments and the following remarks.

Claim Objections

Claim 4 stands objected to for a typographical error which is corrected herewith. Reconsideration and withdrawal of the claim objection are requested.

Information Disclosure Statement

Applicants note that the Examiner has not considered ruled-out art submitted in previous Information Disclosure Statements. Please note that reference "WO 03861567" cited in the Office Action (page 3, top paragraph) should be "WO03061567 A2" Applicants are filing a supplemental Information Disclosure Statement with this reference. With regard to publication dates, the EPO office action cited on October 17, 2007 provided the date of the office action, and the International Search Report filed on December 22, 2005 provided the international filing date. It is the Applicants' understanding that a publication date is not needed. Applicants respectfully request that the art referenced above be considered and a fully initialed PTO Form A820 be returned to the Applicants.

Claim Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 1 and 5-9 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the Specification in such a way as to reasonably convey to one skilled in relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

In making the rejection, the Examiner states "Applicant has disclosed compounds of the formula shown in claim 2, but beyond that applicant has not shown what other compounds would be considered endothelial sphingosine 1-phosphate receptor agonists." (March 4, 2009 Office Action, page 4).

In order to expedite prosecution, Applicants have amended claim 1 to include the structure of claim 2, thus obviating the rejection.

Reconsideration and withdrawal of this rejection are respectfully requested.

Claims 1-9 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement as containing subject matter, which was not described in the Specification in such a way as to reasonably convey to one skilled in relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse this rejection.

In making the rejection, the Examiner states "applicant has not shown their invention such that one of skill in the art at the time of the invention could use the elected species, or any of the compounds encompassed by claim 2 to treat adult (acute) respiratory distress syndrome or other vascular permeability disorders." (March 4, 2009 Office Action, page 5) The Examiner goes on to state "Applicant has demonstrated that FTY720 has some effect on endothelial cell responses in vitro however applicant has not explained how one of skill in the art would translate that to treatment of humans with adult (acute) respiratory distress syndrome. *Id.* The Examiner states "[t]he unpredictability of adult (acute) respiratory distress syndrome is also high, and even more so for treatment of other vascular permeability disorders." (March 4, 2009 Office Action, page 5)

Applicants' Specification teaches that S1P receptor agonists such as FTY720, when phosphorylated, activate vascular S1P receptors and stimulate signaling pathways in a manner similar to S1P. These events result in the inhibition of endothelial cell apoptosis, which occurs in various pathological conditions in which the vascular system is stressed. S1P receptor agonists such as FTY720-P induce adherens junction assembly in endothelial cells leading to blockage of VEGF- induced paracellular permeability *in vitro* and VEGF-induced vascular permeability *in vivo*. The inhibition of vascular permeability by FTY720-P can be applied in

acute vasculopathic situations, such as respiratory distress syndrome which occurs as a complication of sepsis. The connection between FTY720P and vascular permeability is illustrated in the Examples:

- Example 4: Both FTY720-P and (R)-AFD induced an increase in Akt and ERK phosphorylation levels in cultured HUVC cells. Akt protein kinase and ERK protein kinase phosphorylation in endothelial cells and Akt-mediated phosphorylation of $S1P_1$/ EDG-1 receptor are required for S1P-induced migration, an essential element of endothelial cell morphogenesis.
- Example 5: Both FTY720-P and (R)-AFD influence VE-cadherin assembly, which is required to form adherens junctions, critical subcellular structures in endothelial cell morphogenesis and permeability. VEGF-induced paracellular permeability is antagonized by the S1P receptor agonists S1P, FTY720-P and (R)-AFD in an HUVEC system.
- Example 6: FTY720-P or (R)-AFD regulates vascular permeability *in vivo* in a mouse model, by measuring ear vasculature. Phosphorylation of FTY-720 and (R)-AAL by sphingosine kinase *in vivo* and activation of S1P receptors on endothelial cells results in the inhibition of VEGF-induced vascular permeability.

The data presented in the Applicants' Specification clearly demonstrates that VEGF-induced paracellular permeability is antagonized by the S1P receptor agonists S1P, FTY720-P and (R)-AFD in vitro in HUVEC. Applicants also demonstrated that FTY720-P or (R)-AFD regulate vascular permeability *in vivo* in a mouse model, by measuring ear vasculature. Applicants' data clearly shows in accepted in vitro and in vivo animal models that S1P agonists such as FTY720 inhibit vascular permeability. The question is thus whether there is a correlation between the data in the Applicants' Specification and the treatment of disorders associated with vascular permeability disorders such as adult respiratory distress syndrome.

From MPEP 2164.02:

> The issue of "correlation" is related to the issue of the presence or absence of working examples. "Correlation" as used herein refers to the relationship between *in vitro* or *in vivo* animal model assays and a disclosed or a claimed method of use. An

> *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention. If there is no correlation, then the examples do not constitute "working examples." In this regard, the issue of "correlation" is also dependent on the state of the prior art. In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications).
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> Since the initial burden is on the examiner to give reasons for the lack of enablement, the examiner must also give reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model example. A rigorous or an invariable exact correlation is not required, as stated in *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985):
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> > [B]ased upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence. (Citations omitted.)

Applicants respectfully point out that at the time of the invention, acute respiratory distress syndrome was known to be a vascular permeability disorder. As explained in Mortelliti and Manning (Acute Respiratory Distress Syndrome, American Family Physician, 65: 1823-1830, 2002; Attachment A), acute respiratory distress syndrome is characterized by increased capillary permeability. (p. 1823) According to Dudek and Garcia (Cytoskeletal regulation of pulmonary vascular permeability, *J Appl Physiol* 91:1487-1500, 2001; Attachment B), central to inflammatory pulmonary conditions such as acute lung injury, acute respiratory distress syndrome, and sepsis is increased vascular permeability. (p. 1487). As explained in the conclusions, it is "important to identify key regulatory events and effectors responsible for cytoskeletal modulation of pulmonary vascular permeability to hopefully provide a basis for the development of effective therapeutic interventions targeted toward the cytoskeleton." (p. 1495) Because acute respiratory distress syndrome was known to be a vascular permeability disorder, and the Applicants showed that S1P receptor agonists such as FTY720 inhibit vascular permeability, one of skill in the art would have readily understood that vascular permeability

disorders could be treated with S1P receptor agonists such as FTY720. As articulated above, the standard in *Cross v. Iizuka* is not a rigorous correlation, but rather a reasonable correlation. Further, as shown in US Patent No. 6,632,798, the mouse ear model for angiogenesis is an art-accepted model for the inhibitory effect of test compounds on angiogenesis. Given the in vitro and in vivo data presented in the Application, there is a reasonable correlation between the data ad treatment of vascular permeability disorders.

In addition to showing the mechanism of action of S1P agonists, which is directly relevant to its mode of action in acute respiratory distress, the Specification discloses in paragraph [0055] a "suitable daily dosage is about 0.01 to about 10 milligrams per kilogram (mg/kg) per day, or about 0.1 to about 2.5 mg/kg per day, as a single dose or in divided doses" and "unit dosage forms for oral administration comprise about 1 to about 100 mg, or about 5 to about 50 mg active ingredient, e.g. FTY720, together with one or more pharmaceutically acceptable diluents or carriers." Paragraphs [0056]-[0059] describe pharmaceutical formulations.

In sum, Applicants have demonstrated that S1P receptor agonists such as FTY720 are inhibitors of vascular permeability and thus can be used to treat vascular permeability disorders.

Reconsideration and withdrawal of this rejection are requested.

It is believed that the foregoing amendments and remarks fully comply with the Office Action and that the claims herein should now be allowable to Applicants. Accordingly, reconsideration and withdrawal of the objection(s) and rejection(s) and allowance of the case are respectfully requested.

If there are any additional charges with respect to this Amendment or otherwise, please charge them to Deposit Account No. 06-1130.

Respectfully submitted,

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